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Award Number: DAMD17-00-1-0495

TITLE: Lymphedema Prophylaxis Utilizing Perioperative Education

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REPORT DATE: September 2006

TYPE OF REPORT: Final

PREPARED FOR: U.S. Army Medical Research and Materiel Command  
Fort Detrick, Maryland 21702-5012

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REPORT DOCUMENTATION PAGE				Form Approved OMB No. 0704-0188	
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1. REPORT DATE 01-09-2006		2. REPORT TYPE Final		3. DATES COVERED 1 aug 2000 –1 aug 2006	
4. TITLE AND SUBTITLE  Lymphedema Prophylaxis Utilizing Perioperative Education				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER DAMD17-00-1-0495	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S)  Mary Ann Kosir, M.D.				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)  Wayne State University Detroit, MI 48201				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES) U.S. Army Medical Research and Materiel Command Fort Detrick, Maryland 21702-5012				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION / AVAILABILITY STATEMENT Approved for Public Release; Distribution Unlimited					
13. SUPPLEMENTARY NOTES Original contains colored plates: ALL DTIC reproductions will be in black and white.					
14. ABSTRACT The purpose is to evaluate perioperative training for lymphedema assessment and protection. The hypothesis is that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group. The specific questions (scope) are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group? Major Findings: The incidence of lymphedema was 60.1% with a majority occurring within the first year after surgery. Teaching LE protection methods did not reduce the incidence of LE nor improve QOL except at 24 months for those with LE. Those with LE also had increased knowledge of LE protection methods as compared to a control group but only significant at 6 months associated with a booster session. Significance: The LE rate is greater than reported in the literature primarily because prospective measurements were obtained including the first year after surgery when a majority of cases were observed. Other factors that may impact the occurrence of LE without regard to knowledge of protection measures include impaired lymphatic healing after surgery, persistence of activity despite knowing it may cause harm to the extremity, and uncontrolled hypertension which may increase the risk for LE.					
15. SUBJECT TERMS lymphedema, quality of life, education					
16. SECURITY CLASSIFICATION OF:			UU	18. NUMBER OF PAGES  23	19a. NAME OF RESPONSIBLE PERSON USAMRMC
a. REPORT U	b. ABSTRACT U	c. THIS PAGE U			19b. TELEPHONE NUMBER (include area code)

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## INTRODUCTION

### Narrative:

**Subject:** Increasing numbers of breast cancer survivors are at risk for long-term sequelae from treatment. Axillary surgery or radiation therapy to the breast may alter lymph channels, leaving the survivor with a lifetime risk for developing lymphedema. Lymphedema is a swelling of the upper extremity, which causes pain, debility, and reduced quality of life (QOL) that impacts choices about work, social and sexual interactions and self-esteem. Protective measures to reduce the risk of lymphedema become important life-long skills. However, there is inconsistent teaching of protective measures and inattention to lymphedema detection in clinical practice.

**Purpose:** The purpose of this study is to test that structured perioperative training in lymphedema protection will decrease lymphedema, the episodes of infection, the time to detection of lymphedema and improve the QOL in patients undergoing axillary dissection and/or radiation therapy for breast cancer as compared to a control group.

**Scope:** The specific aims are 1) what is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group? 2) What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group? 3) What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group?

**Methods:** Patients with resectable breast cancer also undergoing axillary lymph node surgery and/or radiation therapy to the breast will be prospectively randomized to two groups. In addition to receiving standard care (i.e., written breast rehabilitation materials and preoperative counseling by the breast surgeon), patients in Group 1, will receive structured education in Breast Surgery Rehabilitation including range of motion exercises, lymphedema arm precautions, and management of complications. Patients in Group 2 will receive standard care (written material and preoperative counseling by the surgeon). For both groups, preoperative and then quarterly volume measurements and exams of the upper extremities will be done for three years after surgery in order to determine lymphedema and infection incidence. The QOL will be measured longitudinally by the Functional Assessment of Cancer Therapy-Breast (FACT-B) and the Medical Outcome Study Short Form Health Survey (MOS SF-36) and sexuality subscales of Cancer Rehabilitation Evaluation System (CARES). The knowledge of and practice of lymphedema protective skills will be measured by periodic testing longitudinally as well.

## BODY

Components	
1	Response to Reviewer's comments from previous report
2	Research Accomplishments associated with each task in Statement of Work
3	Table and Figures corresponding to Specific Aims (Supporting Data)
4	Bibliography –Publications and Meeting Abstracts
5	List of Personnel receiving pay from the research effort

**Part 1:**        **Response to Reviewer's comments from Year V report:**  
There were no issues to address. The report was accepted and there were no technical issues.

**Part 2:**        **Research accomplishments associated with each task outlined in the approved Statement of Work. Therefore, the Year V report is cumulative through 8/15/05**  
*(Tables and Figures are clustered after Statement of Work summary)*

**Task 1.**        **Start-up, Months 1-2.**  
This was completely accomplished in 2000.

**Task 2.**        **Introduce study to physicians, nurses and clerks in clinics, Months 1-2.**  
This was completely accomplished in 2000.

**Task 3.**        **Subject recruitment and data collection, Months 3-60.**  
This was completely accomplished.

For the determination of LE and infection rates (Specific Aim 1) in this clinical trial of perioperative education, we report on 163 evaluable participants which meets the goal of at least 158-179 evaluable participants. The analyses of changes in quality of life (QOL) (Specific Aim 2) and determination of knowledge and compliance with LE protection measures (Specific Aim 3) are also based upon this study population.

**Task 4.**        **Perioperative teaching sessions, Months 3-27.**  
This was completely accomplished for all participants in the intervention group. Annual Report IV(Appendix Item #1) showed compliance with this item and will not be repeated in this report.

**Body Part 2 Research Accomplishments associated with each task in Statement of Work (continued)**

**Task 5. Quarterly measurements of subjects, Months 6-60.**

Results for 163 subjects are reported. From the Annual Report Year IV (Appendix Item #3), we showed how the circumference measurement data are recorded in centimeters at multiple standardized sites along both upper extremities. If a patient was unable to complete a quarterly measurement, we saw them at the next opportunity.

**Task 6. QOL questionnaires at 6 months, 1-, 2-, and 3-years postop, Months 9-60.**

QOL data for 163 subjects are reported.

**Task 7. Booster training session for Group 1 subjects, Months 9-33.**

This was completed for all participants in the intervention group. The list was supplied in Annual Report IV (Appendix Item # 2) and will not be duplicated this year.

**Task 8. Knowledge and compliance questionnaires, Months 9-60.**

Knowledge and compliance questionnaires for 163 subjects are reported

**Task 9. Calculations of limb volumes and comparison of differences, Months 3-60.**

Weekly report sheets were created and reviewed which show cumulative data:

- a) volume changes
- b) >1cm measurement changes
- c) symptoms

All subjects with >10% volume change, >1cm measurement change and/or persistent symptoms were evaluated by the LE study nurse. An example of the weekly volume report was in the Annual Report Year IV (Appendix Item # 4) and will not be duplicated this year.

**Task 10. Quarterly data entry and print out by the Psychosocial and Behavioral Core, Months 3-60.**

From the previous annual reports, the Psychosocial and Behavioral Core was dissolved by the reorganization at the Karmanos Cancer Institute. Data entry was performed at least weekly by a data manager through 7/7/05. Backup computer discs were made weekly. After 7/7/05, any remaining data were handled by the PI for entry using a biostatistics core at the cancer institute.

**Task 11. Interim analysis of data after 1 year, 3 years, Months 14-16, 38-40.**

This was accomplished and previously reported for Annual Report IV.

**Task 12. Analysis of data after 5<sup>th</sup> year, Months 61-65.**

The data tables and figures found in **Part 3 of the Body Section** after this section on Statement of Work were performed with the study statistician. The comparisons of various patient characteristics between the control and intervention arm or between patients with and without lymphedema were performed using 2-sample t-tests and chi-square tests. A multivariable logistic regression with a backward variable selection procedure was also utilized to determine the relationship between lymphedema and various risk factors.

**Body Part 2 Research Accomplishments associated with each task in Statement of Work  
(continued)**

**Task 13. Annual report to USAMRMC, Months to be designated by USAMRMC.**  
Completed for each year (I-V) and now Year VI.

**Task 14. Meeting in Baltimore, Maryland to disseminate results of DoD-sponsored Research during the second year, Month to be announced by USAMRMC.**  
Completed. PI attended September, 2003, Orlando, FL. Poster presentation.

**Task 15. Write journal articles. Submit abstract, Months 12-60+**  
Ongoing. Please see Bibliography section (**Part 5 of the Body section**).

**Part 3                      Tables and Figures (Supporting Data)**

**Table 1                      Population Characteristics of Study Participants**

	Intervention Group	Control Group	Univariate
<b>N</b>	<b>78</b>	<b>85</b>	
<b>Mean age, yrs ± S.D.</b>	<b>54.02±11.67</b>	<b>52.86±13.29</b>	<b>P=0.5559</b>
<b>Race</b>			
African American	33.00	35.00	<b>P=1.000</b> <b>For AA</b> <b>Vs Non-AA</b>
Caucasian	38.00	39.00	
Hispanic	1.00	2.00	
Arab/Chaldean	1.00	2.00	
Asian	0.00	4.00	
Native American	2.00	1.00	
Other	3.00	2.00	
<b>Employment status</b>			
Working	31.00	31.00	<b>P=0.7472</b> <b>For working</b> <b>vs. other</b>
Not working	21.00	19.00	
Retired	14.00	12.00	
Not answered	12.00	23.00	
<b>Highest education level</b>			
Less than high school	2.00	2.00	<b>P=0.7235</b>  <b>For College</b> <b>Vs.</b> <b>Non-college</b>
Some high school	8.00	6.00	
High school/GED	40.00	42.00	
Bachelor degree	14.00	15.00	
Masters degree	4.00	8.00	
Doctorate/professional school	3.00	1.00	
Not answered	7.00	11.00	
<b>Annual income</b>			
< \$5,000	6.00	8.00	<b>P=0.4585</b>  <b>For</b> <b>&lt; \$50,000</b> <b>vs.</b> <b>≥ \$50,000</b>
\$5,000-\$15,000	9.00	13.00	
\$15,001-\$30,000	9.00	10.00	
\$30,001-\$50,000	8.00	8.00	
\$50,001-\$75,000	9.00	8.00	
> \$75,001	17.00	15.00	
Not answered	20.00	23.00	
<b>Marital Status</b>			
Divorced/separated	17.00	14.00	<b>P=0.4139</b> <b>For</b> <b>Married/</b> <b>Cohabiting</b> <b>Vs.</b> <b>All others</b>
Married/Cohabiting	38.00	33.00	
Never married	10.00	12.00	
Widowed	9.00	16.00	
Not answered	4.00	10.00	
<b>Transportation</b>			
Usually drive myself	50.00	56.00	<b>P=0.8700</b>  <b>For</b> <b>Drive myself</b> <b>Vs.</b> <b>All others</b>
Usually use public transportation	8.00	2.00	
Usually driven by someone else	15.00	15.00	
Other	0.00	2.00	
Not answered	5.00	10.00	
<b>Religious Preference</b>			
Catholic	21.00	18.00	<b>P=0.5021</b>  <b>For</b> <b>Christian</b> <b>Vs.</b> <b>Non-</b> <b>Christian</b>
Hindu	0.00	1.00	
Jewish	2.00	0.00	
Muslim	1.00	1.00	
Protestant	20.00	20.00	
Other	22.00	30.00	
None	3.00	4.00	
Not answered	9.00	11.00	



**Table 2 Clinical Characteristics of Study Participants in the Intervention and Control Groups for LE Protection teaching.**

	Intervention Group	Control Group	Univariate
<b>N</b>	<b>78</b>	<b>85</b>	
<b>Breast Cancer Stage</b>			<b>P=1.000</b>
0	10.00	8.00	<b>For Stage 0,I vs. Stage IIA,IIB,IIIA,IIIB</b>
I	23.00	29.00	
IIA	19.00	19.00	
IIB	14.00	16.00	
IIIA	7.00	8.00	
IIIB	5.00	5.00	
IV	0.00	0.00	
<b>Type of breast and axillary surgery</b>			<b>P=0.3742</b>
Mastectomy + axillary surgery	40.00	51.00	
Lumpectomy + axillary surgery	33.00	27.00	
Lumpectomy	5.00	7.00	
<b>Radiation therapy</b>			<b>P=0.2442</b>
Yes	56.00	53.00	
No	22.00	32.00	
<b>Number of LNs submitted (mean <math>\pm</math> SD)</b>	<b>8.64<math>\pm</math>6.03</b>	<b>9.63<math>\pm</math>6.23</b>	<b>P=0.3058</b>
= 8 LNs submitted	40(51%)	40(47%)	<b>P=0.6395</b>
> 8 LNs submitted	38(49%)	45(53%)	
<b>Number of LNs positive for ca</b>			
0	45(58%)	48(56%)	<b>P=0.6038</b>
1-3	25(32%)	24(28%)	
>4	8(10%)	13(15%)	
<b>Body Mass Index (BMI) (mean <math>\pm</math> SD)</b>	<b>29.08<math>\pm</math>7.12</b>	<b>28.91<math>\pm</math>7.54</b>	<b>P=0.8882</b>
BMI >25	53(68%)	58(68%)	<b>P=1.000</b>
BMI >30	27(35%)	33(39%)	<b>P=0.6275</b>

**Discussion:** Tables I and II show that the population and clinical characteristics of the study patients for the intervention and control groups show no difference by univariate analysis as expected. This supports the randomization scheme used in the study. Therefore, any differences in LE rate.

**Specific Aim 1:** *What is the incidence of lymphedema and infection during the first three years after surgery among breast cancer patients who received perioperative training in lymphedema protection as compared to a control group?*

**Discussion:** From Table 3A, the of LE in the intervention group is not significantly different from the control group. The initial determination of LE proposed was a greater than 10% volume increase in the extremity as compared to preoperative baseline volume. Since the study began, we have identified additional criteria that are used in practice, including a greater than 1 cm increase in circumference at any measurement site as compared to baseline and as compared to the contralateral extremity. (Published comparison of methods in J Surg Res 2003; please see Part 4 of Body section and Appendix). Table 3B shows the incidence of LE when the criterion of greater than 10% volume increase is used. There is still no difference between the intervention group and the control group. From Table 4, the interim infection rate is similar in the intervention and control groups. However, there are more subjects with infection in the LE group than in the group without LE. This still does not become significant (P=0.1575). Figure 1 depicts the time to appearance of LE. The majority occur within the first year after surgery. Most

persist. Only a minority first occur after the first year of surgery. The time to LE was not different for those in the intervention group or control group. An early paper from this study (J Surg Res 2001; See Part 4 of Body section and Appendix) discussed the appearance of LE within the first year after surgery as well as symptoms preceeding measurement changes by 3 months. The pattern of LE appearance after breast cancer surgery will be presented this Fall, 2005, at the American College of Surgeons (poster session).

**Table 3 A Incidence of LE in the intervention and control groups (Specific Aim 1)**

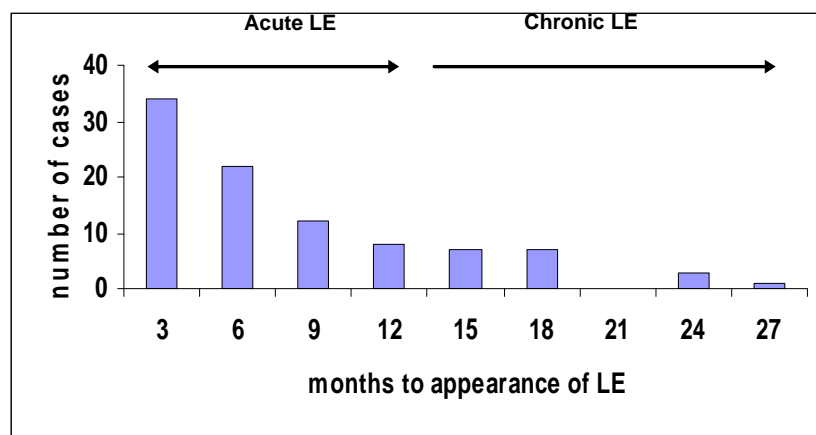
	Secondary LE (n=98)	Without LE (n=65)	P=0.1021
Intervention (n=78)	52 (67%)	26 (33%)	
Control group (n=85)	46 (54%)	39 (46%)	

**Table 3B Incidence of LE in the intervention and control groups (Specific Aim 1)  
(where ARM LE+ determined by >10% volume increase and confirmed by nurse)**

	Secondary LE (n=51)	Without LE (n=110)	P=0.2645
Intervention (n=78)	28 (36%)	50 (64%)	
Control group (n=85)	23 (28%)	60 (72%)	

**Table 4 Infection rate in the intervention and control groups, and in those with LE and without LE (Specific Aim 1)**

Without LE (Specific Aim 1)			
	Infection	No infection	P=0.6150
Intervention (n=78)	4 (5%)	74 (95%)	
Control group (n=85)	3 (4%)	82 (96%)	
LE (n=98)	6 (6%)	92 (94%)	P=0.1575
No LE (n=65)	1 (2%)	64 (98%)	



**Fig. 1. Determining when secondary LE occurs after breast cancer surgery.** Using quarterly prospective upper extremity measurements after breast cancer surgery, determination of secondary LE was made by comparing volume changes to preoperative measurements. These were verified by a LE nurse specialist. The months to appearance of secondary LE are along the x-axis, and number of cases along the y-axis. By definition, acute LE presents and resolves within 12 months. Chronic LE presents after 12 months, or, if acute LE persists after 12 months, it is then considered chronic.

**Table 5 Population Characteristics of Breast Cancer Survivors with and without Upper Extremity Secondary Lymphedema (LE) (Specific Aim 1)**

	With LE	Without LE	Univariate
<b>N</b>	<b>98</b>	<b>65</b>	
<b>Mean age, yrs±SD(range)</b>	<b>52.7±13.8</b>	<b>53.0±13.9</b>	<b>P=0.8954</b>
<b>Race</b>			<b>P=0.7744 For AA Vs Non-AA</b>
African American	40	28	
Caucasian	45	32	
Hispanic	3	0	
Arab/Chaldean	3	0	
Asian	1	3	
Native American	1	2	
Other	5	0	
<b>Employment status</b>			<b>P=0.6586 For working vs. other</b>
Working	39	23	
Not working	21	19	
Retired	18	8	
Not answered	20	15	
<b>Highest education level</b>			<b>P=0.7999 for College Vs. Non-College</b>
Less than high school	11	7	
High school/GED	49	33	
Associate degree			
Bachelor degree	18	11	
Masters degree	7	5	
Doctorate/professional school	3	1	
Not answered	10	8	
<b>Annual income</b>			<b>P=0.1484 for &lt; \$50,000 Vs. ≥ \$50,000</b>
< \$5,000	7	7	
\$5,000-\$15,000	12	10	
\$15,001-\$30,000	11	8	
\$30,001-\$50,000	10	6	
\$50,001-\$75,000	13	4	
> \$75,001	21	11	
Not answered	24	19	
<b>Marital Status</b>			<b>P=0.2860 For Married/ Cohabiting Vs. others</b>
Divorced/separated	19	12	
Married/Cohabiting	47	24	
Never married	14	8	
Widowed	12	13	
Not answered	6	8	
<b>Transportation</b>			<b>P=0.4150 for Drive myself Vs. All others</b>
Usually drive myself	63	43	
Usually use public transportation	8	2	
Usually driven by someone else	20	10	
Other	0	2	
Not answered	7	8	
<b>Religious Preference</b>			<b>P=0.1230 For Christian Vs. Non- Christian</b>
Catholic	25	14	
Hindu	0	1	
Jewish	1	1	
Muslim	2	0	
Protestant	27	13	
Other	29	23	
None	2	5	
Not answered	12	8	

**Table 6 Clinical Characteristics of Breast Cancer Survivors with and without Secondary LE**

	With LE	Without LE	Univariate
<b>N</b>	<b>98</b>	<b>65</b>	
<b>Breast Cancer Stage</b>			<b>P=0.0220</b>
0	5	13	<b>For Stage 0,I vs. Stage IIA,IIB,IIIA,IIIB</b>
I	30	22	
IIA	25	14	
IIB	21	9	
IIIA	10	5	
IIIB	7	2	
IV	0	0	
<b>Type of breast and axillary surgery</b>			<b>P=0.0668</b>
Mastectomy with axillary surgery	53	38	
Lumpectomy with axillary surgery	41	19	
Lumpectomy	4	8	
<b>Radiation therapy</b>			<b>P=0.8741</b>
Yes	66	43	
No	32	22	
<b>Number of LNs submitted (mean ± SD)</b>	<b>11.3±6.1</b>	<b>6.2±5.2</b>	<b>P&lt;0.0001</b>
= 8 LNs submitted	33	47	<b>P&lt;0.0001</b>
> 8 LNs submitted	65	18	
<b>Number of LNs positive for ca</b>			
0	50	46	<b>P=0.0297</b>
1-3	33	11	
>4	14	7	
<b>Body Mass Index (BMI) (mean ± SD)</b>	<b>29.5±7.2</b>	<b>28.2±7.3</b>	<b>P=0.2804</b>
<b>BMI Groups</b>			<b>P=0.5906</b>
Normal: BMI = 25	26	22	
Overweight: 25<BMI = 30	35	20	
Obese: BMI >30	37	23	

**Discussion:** From Tables 5 and 6, univariate analysis of those with LE compared with those without LE showed that LE was significantly associated with certain clinical characteristics. From Table 6, these included the number of mean number of lymph nodes resected at surgery especially if >8 lymph nodes were submitted ( $P<0.0001$ ). Furthermore, while the mean number of lymph nodes positive for metastatic cancer was associated with increased risk for LE, ( $p=0.0297$ ). There was also increased risk of LE with higher stage of breast cancer (Stage IIA and above vs Stage 0 or I,  $p=0.0220$ ) which supports the date for lymph nodes removed and number of lymph nodes positive. There were no population characteristics associated with those with increased risk of LE from Table 5. Income and education are not significant for the occurrence of LE.

**Table 7 Logistic Regression – Odds Ratio Estimates**

Model: Lymphedema = BMI &gt; 25 Control arm Ln submitted Ln positive Mastectomy Radiotherapy

Patient Factor	Odds Ratio	95% CI Lower Limit	95% CI Upper Limit	P-Value
BMI>25 vs. BMI = 25	1.051	0.484	2.280	0.9006
Control vs. Intervention	0.553	0.266	1.149	0.1124
# nodes submitted = 9 vs. < 9	5.915	2.729	12.821	<.0001
# Positive Nodes = 1 vs. 0	2.406	1.099	5.267	0.0281
Mastectomy vs. Other	0.377	0.142	1.003	0.0507
Radiotherapy vs. None	0.721	0.274	1.901	0.5083

**Discussion:** To investigate whether there are any variables more strongly associated with LE, multivariate analysis was performed. For multivariate analysis, stepwise logistic regression using the backward selection method was performed to determine association with LE by variables in the clinical or population characteristics. LE (yes/no) was dependent, and the other variables were explanatory variables. From Table 7, the highest correlation with developing LE was with any lymph nodes positive (p=0.0281) or the number of lymph nodes removed at surgery (<0.001). Being in the education control arm did not correlate with higher LE (or being in the intervention arm did not correlate with lower risk for LE). BMI greater than 25, and undergoing radiation therapy did not increase the risk for LE.

**Specific Aim 2:** *What are the differences in the measured QOL among breast cancer patients during the first three years after surgery that received perioperative education in lymphedema protection as compared to a control group?*

**Discussion:** Table 8a compares quality of life scores for the intervention group and control group beginning with baseline using standardized instrument: FACT-B, MOS-SF-36, and the sexual and marital subscales of CARES. Although the prospective randomization of participants into intervention and control groups was as expected, it appears as if baseline QOL scores for Fact B are not similar. The reason for this is unclear, and was not a criterion for prospective randomization. The MOS-SF 36 has comparable scores among the groups at baseline, using the Physical and Mental subscales. Neither the FACT-B or MOS-SF-36 are specific for LE, but ask about function and body image. Not all subjects are willing to answer the CARES questionnaire asking about marital and sexual relationships. Those questionnaires with >75% of questions answered were used in the analysis. Baseline responses are similar.

In Table 8b, the quality of life scores were grouped based on LE status at the time of the questionnaire. The only significant difference noted was at 24 months using the MOS-SF-36 instrument. The physical scale shows improved quality of life for those with LE as compared to those without. We observed that some subjects with LE resolved, up to 40% if they developed acute LE. This improvement in quality of life may reflect that observation, although the study

was not designed to determine resolution or diminution of LE. This would be the subject of another study.

**Table 8a Quality of life scores comparing the Intervention and Control groups (Specific Aim 2)**

	Intervention group	Control group
<b>Fact –B Total Scores (Total)</b>		
initial mean (n)	123.49 (69)	105.84 (76)
6-month mean (n)	124.69 (53)	114.61 (48)
12-month mean (n)	126.71 (40)	115.70 (49)
24-month mean (n)	126.87 (19)	134.43 (23)
36-month mean (n)	98.50 (13)	121.36 (20)
<b>MOS SF-36 - Physical Scale</b>		
initial mean (n)	45.46 (68)	49.49 (68)
6-month mean (n)	42.08 (52)	36.02 (47)
12-month mean (n)	46.91 (44)	44.32 (45)
24-month mean (n)	45.59 (19)	48.54 (22)
36-month mean (n)	43.62 (14)	46.49 (19)
<b>MOS SF-36 - Mental Scale</b>		
initial mean (n)	49.76 (68)	45.37 (68)
6-month mean (n)	57.29 (52)	61.28 (47)
12-month mean (n)	48.48 (44)	52.51 (45)
24-month mean (n)	51.82 (19)	51.60 (22)
36-month mean (n)	49.67 (14)	50.14 (19)
<b>CARES- Sexuality Subscale</b>		
initial mean (n)	46.73 (59)	48.93 (58)
6-month mean (n)	47.54 (46)	47.83 (40)
12-month mean (n)	48.32 (31)	48.55 (44)
24-month mean (n)	47.43 (14)	48.47 (19)
36-month mean (n)	50.00 (10)	49.13 (15)
<b>CARES- Marital Subscale</b>		
initial mean (n)	48.46 (59)	51.57 (58)
6-month mean (n)	49.78 (46)	50.20 (40)
12-month mean (n)	50.94 (31)	51.00 (44)
24-month mean (n)	49.36 (14)	51.16 (19)
36-month mean (n)	53.20 (10)	49.93 (14)

**Table 8b**      **Quality of life (QOL) scores comparing those with and without LE (Specific Aim 2)**

	With LE	Without LE
<b>Fact –B Total Scores (Total)</b>		
6-month mean (n)	111.63 (33)	122.47 (71)
12-month mean (n)	120.11 (43)	118.19 (52)
24-month mean (n)	132.13 (24)	129.52 (18)
36-month mean (n)	110.77 (20)	114.39 (17)
Last Follow-up mean (n)	117.06 (96)	113.31 (63)
<b>MOS SF-36 Physical Scale</b>		
6-month mean (n)	31.74 (32)	43.29 (61)
12-month mean (n)	47.79 (37)	43.26 (47)
24-month mean (n)*	50.21 (21)	43.97 (20)
36-month mean (n)	43.08 (16)	46.27 (14)
Last Follow-up mean (n)	43.52 (84)	42.12 (57)
<b>MOS SF-36 Mental Scale</b>		
6-month mean (n)	68.37 (32)	54.28 (61)
12-month mean (n)	48.30 (37)	54.21 (47)
24-month mean (n)	53.13 (21)	50.14 (20)
36-month mean (n)	49.08 (16)	49.29 (14)
Last Follow-up mean (n)	49.85 (84)	49.01 (57)
<b>Sexuality Subscale</b>		
6-month mean (n)	49.04 (46)	50.77 (13)
12-month mean (n)	50.14 (37)	50.04 (23)
24-month mean (n)	52.10 (10)	48.55 (11)
36-month mean (n)	49.75 (4)	51.86 (14)
<b>Marital Subscale</b>		
6-month mean (n)	51.80 (45)	53.59 (17)
12-month mean (n)	52.00 (36)	53.16 (25)
24-month mean (n)	54.64 (11)	52.00 (13)
36-month mean (n)	53.00 (4)	53.25 (12)

***Specific Aim 3)** What are the retention of information on lymphedema protection, and the compliance with arm precautions among breast cancer patients who received perioperative lymphedema training as compared to a control group?*

**Discussion:** As a review, the knowledge questionnaires were given preoperatively and at 6 months, 12 months, 24 months and 36 months after surgery. There are 17 questions that cover several categories of protection methods to reduce the risk of LE. They are scored either 0 or 1 and the Total Score is just the proportion marked 1. This year, the score was multiplied by 100 to give a score from 1-100. The compliance questionnaires are given at the same intervals as the knowledge questionnaires with the exception that no preoperative compliance questionnaire is given. There are 22 questions with each scored from 0 to 4 depending on the frequency of use of a particular protection method. Total Score is the sum of these values divided by the number of questions answered.

In addition to the total score for each questionnaire, responses to groups of questions that correspond to specific protection measures are shown this year in Table 9. Even though none of these measures show a statistical significance between arms, one can see that the differences grow larger with time. The insignificant results are mostly due to the small sample sizes in the later time points.

In Table 10, when comparing those with LE to those without LE, there were significantly more items identified as protection measures in those who had LE as compared to those without LE ( $p=0.0024$ ). For all intervals, it appears that those with LE score better on the knowledge questionnaire although it is not significant. It appears that those with LE also show better compliance with protection measures as compared to the control group, but this also is not significant. There may be improvement in the knowledge of LE once a patient has the condition.



**Table 9 Knowledge scores (0-100 scale) and Compliance scores (0-4 scale) comparing Intervention and control groups (Specific Aim 3)**

KNOWLEDGE QUESTIONNAIRE		CATEGORY AND INTERVAL	COMPLIANCE QUESTIONNAIRE	
Intervention group	Control group		Intervention group	Control group
Total Score				
36.99 (n=79)	35.08 (n=70)	initial mean	n.a.	n.a.
64.68 (n=56)	60.24 (n=51)	6-month mean	3.27 (n=52)	3.16 (n=45)
71.98 (n=45)	69.73 (n=49)	12-month mean	3.07 (n=43)	3.03 (n=47)
75.93 (n=21)	72.22 (n=23)	24-month mean	2.98 (n=19)	3.18 (n=24)
79.49 (n=13)	67.46 (n=21)	36-month mean	2.96 (n=15)	3.02 (n=21)
Protection from Injury				
38.48	36.29	initial mean	n.a.	n.a.
71.07	61.57	6-month mean	3.33	3.12
74.22	75.10	12-month mean	3.02	2.99
76.19	75.65	24-month mean	3.02	3.11
83.08	71.43	36-month mean	2.69	3.09
Protection from Infection				
44.94	45.00	initial mean	n.a.	n.a.
76.79	75.49	6-month mean	3.71	3.76
85.56	86.74	12-month mean	3.58	3.61
92.86	80.44	24-month mean	3.74	3.50
96.15	83.33	36-month mean	3.50	3.58
Protection from Overheating				
31.65	27.14	initial mean	n.a.	n.a.
71.43	47.06	6-month mean	3.41	3.24
75.56	65.31	12-month mean	3.21	3.10
80.95	73.91	24-month mean	3.22	3.38
84.62	61.91	36-month mean	3.20	3.10
Protection from Overexertion				
46.20	44.29	initial mean	n.a.	n.a.
75.00	74.51	6-month mean	3.12	3.10
78.89	83.67	12-month mean	3.09	3.12
85.71	86.96	24-month mean	2.73	3.11
84.62	83.33	36-month mean	2.94	3.09
Protection from Constriction				
44.62	40.71	initial mean	n.a.	n.a.
70.98	72.06	6-month mean	3.40	3.14
77.22	73.47	12-month mean	3.19	3.14
79.76	80.44	24-month mean	3.07	3.45
80.77	70.24	36-month mean	3.46	3.07

**Table 9 Knowledge and compliance questionnaire scores comparing those with LE and those without LE (Specific Aim 3)**

	With LE	Without LE
<b>Knowledge Questionnaire</b>		
initial mean(n)	44.39 (77)	31.52 (81)
6-month mean(n)	72.72 (69) *	57.80 (46)
12-month mean(n)	77.29 (50)	72.06 (40)
24-month mean(n)	83.76 (25)	74.51 (18)
36-month mean(n)	85.17 (23)	57.84 (12)
<b>Compliance Questionnaire</b>		
6-month mean(n)	3.26 (63)	3.04 (40)
12-month mean(n)	3.12 (54)	2.89 (38)
24-month mean(n)	3.28 (26)	2.77 (17)
36-month mean(n)	3.12 (23)	2.69 (11)

\* Statistically significant at the overall experiment-wise error level of .05 (p-value=0.0024)

## **Part 4            Bibliography**

### **Publications**

Kosir, M.A., Rymal, C., Koppolu, P., Hryniuk, L., Darga, L., Du, W., Rice, V., Mood, D., Shakoor, S., Wang, W., Bedoyan, J., Aref, A., Biernat, L Northouse, L. Surgical Outcomes after Breast Cancer Surgery: Measuring Acute Lymphedema. J Surg Res 95:147-151, 2001.

Bland, K.L., Perczyk, R., Du, W., Rymal, C., Koppolu, P., McCrary, R. Kosir, MA Can a practicing surgeon detect early lymphedema reliably? Am J Surg., 186:509-513, 2003.

Mehmood, S., Faris, R., Edelman, D., Kosir, M.A. Equality in male breast cancer care using sentinel lymph node biopsy. Am J Surg, Submitted, 2004.

O'Connor S, Du W, Perczyk R, Rymal C, Ranella M, Pawlowski D, Kosir MA. Poorly Controlled Hypertension as a Co-Morbid Condition Affection Lymphedema Risk in Breast Cancer Surgical Patients. Am J Surg, Submitted 2005.

Francis WP, Abghari P, Du W, Rymal C, Suna M, Kosir MA. Improving Surgical Outcomes: Sentinel Lymph Node Biopsy Reduces the Severity of Postoperative Acute Lymphedema., Am J Surgery, In Press, 2006.

### **Meeting Abstracts/Presentations**

2000 "Surgical Outcomes after Breast Cancer Surgery: Measuring Acute Lymphedema", 24<sup>th</sup> Annual Surgical Symposium, Association of VA Surgeons, Seattle, WA. (Accepted abstract; oral presentation)

2002 Lymphedema Prophylaxis Utilizing Perioperative Education. Department of Defense Breast Cancer Research Program Meeting "Era of Hope" , Orlando, FL. (Poster presentation)

Kosir, M.A., Rymal C., Du, W., Koppolu, P., Smith, D., Mood, D., Rice, V., Northouse, L., Aref, A., Brown, M., Youssef, E. Lymphedema Prophylaxis Utilizing Perioperative Education. Department of Defense Breast Cancer Research Program Meeting "Era of Hope" Proceedings III:P58-9, 2002 (Abstract)

2002 "Does the Extent of Breast Cancer Surgery Impact Sexual and Marital Aspects of Quality of Life?", 93<sup>rd</sup> Annual Meeting, American Association for Cancer Research, San Francisco, CA. (Poster presentation)

Kosir, M., Du, W., Smith, D., Rymal, C., McCrary, R., Koppolu, P., Parlapalli, M., Shakoor, S., Brown, M., Newman, L., Carolin, K., Bouwman, D., White, M., Foley-Loudon, P. Does the Extent of Breast Cancer Surgery Impact Sexual and Marital Aspects of Quality of Life? Proceedings of the American Assoc for Cancer Res 43:821, 2002. (Accepted abstract)

2003 Lymphedema Detection by Circumferential Measurements, 5<sup>th</sup> Annual Lynn Sage Breast Cancer Symposium, Chicago, IL. (Accepted abstract; poster presentation)

- 2003 Can a Surgical Practice Detect Lymphedema? 27<sup>th</sup> Annual Surgical Symposium, Association of VA Surgeons, Nashville, TN. (Accepted abstract; oral presentation).
- 2004 Equality in Male Breast Cancer Care Using Sentinel Lymph Node Biopsy, 28<sup>th</sup> Annual Surgical Symposium, Association of VA Surgeons, Richmond, VA. (Accepted abstract; poster presentation).
- 2004 Kosir, MA, Rymal, C, Perczyk, R, O'Connor S, Koppolu P, Du W, Smith D, Pawlowski D. "When does lymphedema occur after breast cancer surgery?" 6<sup>th</sup> Annual Lynn Sage Breast Cancer Symposium Proceedings, 2004 (Accepted abstract and poster presentation).
- 2005 Poorly Controlled Hypertension as a Co-Morbid Condition Affection Lymphedema Risk in Breast Cancer Surgical Patients, 29<sup>th</sup> Annual Surgical Symposium, Association of VA Surgeons, Richmond, VA. (Accepted abstract; oral presentation).
- 2005 Education, knowledge and behavior change among breast cancer survivors with lymphedema. Society for Applied Anthropology, Santa Fe, New Mexico (Accepted abstract; oral presentation).
- 2005 Clinical Patterns of Lymphedema After Breast Cancer Surgery: When Does It Occur? American College of Surgeons 2005 Clinical Congress, San Francisco, CA (Accepted abstract; Scientific exhibit).
- 2006 Improving Surgical Outcomes: Sentinel Lymph Node Biopsy Reduces the Severity of Postoperative Acute Lymphedema.,30<sup>th</sup> annual Surgical Symposium, Association of VA Surgeons, Cincinnati, OH. Oral presentation.

**Part 5            List of Personnel receiving pay by this research effort**

Aref, A  
Balon, J  
Bedoin, J  
Bey-Knight, L  
Bohler-Collins, D  
Brown, M  
Darga, L  
Du, W  
Foley, P  
Gonik, N  
Hryniuk, L  
Jain, V  
Kimler, V  
King, S  
Koppolu, P  
Kosir, M  
Liguminati, S  
Northouse, L  
O'Connor, S  
Parlapalli, M  
Perczyk, R  
Rymal, C  
Smith, D  
St.Onge, K  
Tang, G  
Wang, W

## KEY RESEARCH ACCOMPLISHMENTS

- A 2001 article was published and presentation made at a national meeting that documented lymphedema within the first year after breast cancer surgery as well as symptoms of LE preceeding measurement changes by 3 months (J Surg Res 95:147-151, 2001). The article was cited by Dr. Armer and a collaboration formed to standardize the symptom reporting for LE. Two additional presentations at national meetings showed the patterns of LE occurrence from interim data.
- A 2003 article (Am J Surg., 186:509-513, 2003) was published and presentation made at a national meeting that compared various methods and standards for defining LE in the literature. Using the methods in this study as the “gold standard”, the use of a 5% volume or circumference change had a high positive predictive value for identifying LE. This method can be taught to surgical practices so that preoperative measurements can be obtained and postoperative visits can repeat these measurements to simplify identification of those who should be referred to a LE expert.
- A 2004 article was submitted and presented as poster at a national meeting regarding the sentinel lymph node biopsy in men. Two men were enrolled in this study and one developed LE and the other did not. Both underwent the sentinel lymph node biopsy. Article not accepted for publication however.
- A 2005 article was submitted and presented at a national meeting that correlated uncontrolled hypertension with development of LE using a prospective measurement collection method, unlike that previously reported in the literature. These findings have been incorporated into a funded study where the influence of blood pressure control on the occurrence of LE is being studied. Article was not accepted for publication however.
- A 2006 article is in press (Am J Surg, 2006) as a result of the acceptance of abstract for presentation at a national meeting. It reported the rate of LE in those with sentinel lymph node biopsy compared to those with axillary dissection using the CTCAE v.3 criteria where a 5% volume increase or 5% increase in circumference at any point along the arm was considered the threshold for LE detection. This dissemination of this information to the clinical area is very important. The surgeons at the meeting were quite surprised how overlooked this could be. It may impact surgical practice, we hope.

## REPORTABLE OUTCOMES

### ---Manuscripts and presentations

Please see bibliography in **Part 4 of Body** of this report and **Appendix**.

### ---Funding Applied

Komen Foundation Postdoctoral Fellowship Research Award, “Increased Incidence of Lymphedema in African American and Hispanic Breast Cancer Patients”, submitted 8/03, not funded.

\$261,251 (PI), WSU Research Enhancement Program, “Looking for Answers in Lymphedema Prevention: Is it what we inherit? Is it what we do? Is it what we treat?”, 5/1/05-4/30/07.

\$250,000 (PI), Komen Foundation, “Linking Lymphedema to Disorders of Lymphangiogenesis”, 5/1/05-4/30/07.

NIH, “Linking Lymphedema to Disorders of Lymphangiogenesis”, submitted 6/04, revised and resubmitted 07/06.

## CONCLUSIONS

- **Lymphedema was detected in 60.1% of participants who underwent breast cancer surgery using prospective arm circumference measurements and volume determinations for the upper extremities.**
- **The incidence of LE and infection did not differ for those breast cancer patients who received perioperative training in lymphedema protection as compared to a control group (Specific Aim 1). The possibilities: the training needs to be re-formatted, or there are other influences on the development of LE despite knowledge of protection methods (Specific Aim 3). The latter is the basis of two funded grants emanating from this project investigating inherited defects in lymphangiogenesis genes, the effect of activities, and the effect of uncontrolled hypertension.**
- **A majority of LE cases occurred within the first year after breast cancer surgery (78.4%). Furthermore, a majority of cases persisted after the first year.**
- **The quality of life as affected by LE is not measured by FACT-B or MOS-SF 36. This led to the inclusion of qualitative interviews in a funded grant whereby study participants are asked about barriers to compliance with LE protection methods.(Specific Aim 2).**

## "So What Section"

There has been resurgence in the interest of lymphedema as evidenced by new funding opportunities for researchers. However, the awareness of lymphedema occurrence, protection, and treatment by many clinicians that are in contact with breast cancer survivors is not uniform. As a result of this research project, this group has had the opportunity to present at national meetings. The latest were at the American College of Surgeons Annual Clinical Congress in October, 2005, and at the Association of VA Surgeons in May, 2006. This is significant because lymphedema is a consequence of treatment for breast cancer, including surgery of the axilla. This provides an excellent forum to discuss findings and possibly influence surgical practice.

## REFERENCES

n.a.

## APPENDIX—n.a.

## SUPPORTING DATA

Please see **Part 3 of Body** of this report for Tables and Figures.